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The impact of F-18 FDG PET/CT in the restaging of colorectal cancer in patients with suspected recurrence

Kolorektal kanserlerin yeniden evrelemesinde F-18 FDG PET/BT'nin önemi

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ABSTRACT

Aim: The aim of the present study is to investigate the impact of F-18 FDG PET/CT in the restaging of colorectal cancer in patients with suspected recurrence. Thus, PET/CT findings were compared with that of CT. In addition, the correlation between serum CEA levels and PET/CT and CT findings was investigated. Furthermore, the role of PET/CT in treatment response among patients who were treated after restaging was assessed.

Material and Method: In this retrospective study, a total of 102 patients operated for colorectal cancer (63 female, 39 male, mean age 65.81±4.63 years) were investigated. F-18 FDG PET/CT scans were acquired in all patients. The findings of PET/CT were compared with that of concurrent CT, and also with CEA levels.

Results: In the study, the success rates of PET/CT and CT in detecting pathologic lesions in colorectal cancer cases with suspected recurrence were 98% and 64.7%, respectively. In 34 cases, pathologic lesions were detected with PET/CT, while CT showed no recurrence. The lesions of 68 cases out of 70 with high CEA levels were localized by means of PET/CT, whereas pathology was observed by CT in only 45 cases. Thus, PET/CT was considered more successful than CT in detecting recurrence. In the liver where lesion was localized the most, the sensitivity and specificity of PET/CT were 88% and 92%, respectively, while the sensitivity and specificity of CT were 80% and 76%, respectively.

Conclusion: In the light of findings, our study suggested PET/CT as a valuable imaging tool for restaging and treatment response assessment in colorectal cancer cases with suspected recurrence.

Keywords: Colorectal cancer, F-18 FDG PET/CT, CT, restaging

ÖZ

Giriş: Bu çalışmada, kolorektal kanserli hastalarda, uygulanan cerrahi, kemoterapi, radyoterapi sonrası takip döneminde hastalığın nüksünü düşündürür belirti ve bulgu varlığında nüksü doğrulamak ve hastalığın yayılım bölgelerini saptamak için yapılan yeniden evrelemede F-18 FDG PET/BT'nin öneminin saptanması amaçlanmıştır. Bunun için PET/BT görüntüleri, BT görüntüleri ile karşılaştırılmış ve serum CEA düzeyi ile görüntüleme yöntemlerinin uyumu incelenmiştir. Ayrıca, yeniden evrelemede patolojik bulgu saptanan hastalarda uygulanan tedavi sonrası tedaviye cevabın belirlenmesinde PET/BT'nin rolü de araştırılmıştır.

Gereç ve Yöntem: Retrospektif olarak yapılan bu çalışmaya, 102 hasta dahil edilmiştir. Tüm hastalara yeniden evrelendirme amacıyla F-18 FDG ile PET/BT görüntülemesi yapılmış olup PET/BT sonuçları, eş zamanlı olarak yapılan BT, serum CEA düzeyi ve klinik, eğer varsa histopatolojik incelemenin sonuçları ile karşılaştırılmıştır.

Bulgular: Çalışmada, nüks şüphesi olan kolorektal kanserli olgularda, PET/BT'nin patoloji saptama oranı %98, BT'nin ise %64,7 olarak hesaplanmıştır. BT'de patoloji izlenmeyen 34 hastada PET/BT ile patolojik lezyonların görüntülenebildiği, serum CEA düzeyi normal olan 70 hastanın 68'inde PET/BT ile, 45'inde ise BT ile patolojik lezyonun lokalize edildiği görülmüştür. Yapılan değerlendirmede, nüks hastalığın saptanmasında PET/BT'nin BT'den daha başarılı olduğu sonucuna ulaşılmıştır.

Sonuç: Bu bilgiler ışığında, takip döneminde nüks şüphesi olan kolorektal kanserli olguların yeniden evrelemesinde ve sonrasında yapılan tedavinin etkinliğinin değerlendirilmesinde F-18 PET/BT'nin yararlı olduğu sonucuna ulaşılmıştır.

Anahtar Kelimeler: Kolorektal kanser, PET/BT, BT, yeniden evreleme

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INTRODUCTION

Colon and rectum cancers classified as colorectal cancers are substantial health problems, mostly seen in developed countries, which result in severe morbidity and mortality. In general, colorectal cancer is diagnosed between 50-75 years of age, and aging is a major risk for the disease. Lymphatic dissemination is the most common way of metastatic spread and the most common sites of metastasis are the liver (60%), the lung (50%), the bone (15%), and the peritoneum (15%) (1-3).

The treatment of colorectal cancer depends on tumor location and size, and the overall health condition of the patient. The standard treatments are surgery, chemotherapy, and radiotherapy. Recurrence in colorectal cancer occurs in the first 4 years after surgery, generally with liver occupancy (4-10). In case of the presence of pathological focus or signs and symptoms for suspected recurrence, restaging is important in order to decide on the treatment plan and to determine the extent of the disease (3-7).

PET/CT is a widely preferred hybrid imaging modality for restaging in oncological patients. The superiority of PET/CT over other imaging modalities lies in its ability to spot metabolic/functional changes at early stages in the absence of morphological changes. Early detection of tumors with PET/CT scan leads to early treatment and prolonged survival (8-14).

F-18 FDG PET/CT is commonly used for staging, restaging, treatment response assessment, radiotherapy planning, and chemosensitivity assessment in many types of cancer (14-19).

The present study aims to investigate the impact of F-18 FDG PET/CT in the restaging of colorectal cancer in patients with suspected recurrence, as well as determining the extent of the disease.

MATERIAL AND METHOD

Patients

A total of 102 patients with colorectal cancer who were referred to Başkent University Adana Research Hospital Nuclear Medicine Department between January 2007 and December 2011 for restaging PET/CT scan due to suspected recurrence were included in the study. Data were retrospectively collected from the medical records of these patients.

PET/CT results were compared with that of CT, which is also widely used in the diagnosis, and follow-up evaluation of oncologic patients. The correlation between serum CEA levels and the imaging modalities was also investigated. The results were confirmed with histopathological data where available (n=30), or, alternatively, with clinical follow-up.

In the presence of pathological evidence on the restaging imaging, the importance of PET/CT in treatment response was assessed. Changes in the SUV levels of lesions were also noted in this regard.

Due to the regulations and the requriements which are subject to our study at the date of appication did not enforce seperate ethical approval for retrospective studies. Our study was approved by Başkent University Medicine and Health Sciences Research Board of the institution within these circumstances that are explanied above (Date: 02.08.2011, Decision No: KA11/166). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

PET/CT Imaging

Blood glucose levels were checked before the procedure. Patients whose blood glucose levels less than 200 mg/dl were administered 9-15 mCi F-18 FDG via the intravenous route. Then, the patients rested for approximately an hour in a calm environment without speaking or chewing anything until the imaging procedure.

The scanner used in the study was GE Discovery STE 8 Slice PET/CT (General Electric Company, Milwaukee, Wisconsin, USA) with retractable septa and a 17 cm field-of-view (FOV). Trans-axial resolution was 5.47 mm in 2D mode and 6 mm in 3D mode. Imaging was performed while patients were in the supine position with their arms up or next to the body and asked to breathe normally. After topographic CT imaging, vertex-to-upper-thigh CT images were acquired with 80mA chamber current and 140kV chamber voltage at 0.8-second rotation speed. Immediately following CT imaging, PET imaging was performed for 3-4 minutes per bed position. Scatter and attenuation correction of both CT and PET images were done. Maximum Intensity Projection (MIP), and PET, CT, and PET/CT fusion images were acquired.

F-18 FDG PET/CT images were examined in the light of diagnosis, administered treatment history, results and other imaging scans where available, and laboratory findings. In addition, the presence of focal lesion with increased FDG uptake, and the size and presence of a CT counterpart of the lesion were investigated. Lesions were examined for malignancy by considering physiological uptakes, typical presentation characteristics of benign formations, and fusion images. In the semi-quantitative assessment of lesions, the standard uptake value (SUV) of FDG was used.

Statistical Analysis

Statistical analysis was performed with SPSS version 15.0 (Statistical Package for Social Sciences, IBM Company). Descriptive statistics were used. Chi-squared and

Fischer's exact tests were conducted for comparisons between groups. The results were presented in 2 by 2 tables. P < 0.05 was considered as statistically significant.

A total of 102 patients with colorectal cancer were included in the study; 39 (38.2%) were male and 63 (61.8%) were female. The mean age of the patients was 65.81±4.63 years. All patients had undergone surgery following the diagnosis, and staging steps and chemotherapy was administered. The follow-up time was 11 to 50 months. During the follow-up period, all patients underwent restaging in order to determine the dissemination of the disease, as there were signs and symptoms suggesting recurrence. The time to recurrence was 6 months to 2 years. For restaging, all 102 patients underwent PET/CT, and 101 had a CT scan.

PET/CT and CT Results and Restaging

The pathologic lesion detection rate of PET/CT for restaging purposes was determined as 98%. Upon the examination of results, activity uptake was found in the liver (n=45), lung (n=41), pelvic lymph nodes (n=27), rectosigmoidal lymph nodes (n=25), surgical site (n=23), mediastinum (n=21), abdomen (n=19), mesenteric lymph nodes (n=13), head and neck (n=11), reptoperitoneal lymph nodes (n=11), bone (n=9), supraclavicular lymph nodes (n=7), suprarenal gland (n=4), kidney (n=2), para-aortic lymph nodes (n=2), gastric lymph nodes (n=2), hilus (n=1), anal area (n=1) and peritoneum (n=1). Localization of pathology detected sites with PET/CT and avarage SUV values are repsented in **Table 1**. PET/CT and CT agreement for lung, liver and surgery area are presented in **Table 2**.

Table 1. Localization of pathology detected sites with PET/CT and average SUV values

Localization	PET/CT (n=102)	SUV* (avr±SD)
Mediastinum	20.6% (n=21)	3.71±2.51
Hilus	1% (n=1)	5
Lung	40.2% (n=41)	6.96±3.56
Liver	44.1% (n=45)	9.80±7.29
Gastric LN†	2% (n=2)	9.50±3.54
Retroperitoneal LN†	10.8% (n=11)	5.91±4.25
Pelvic LN†	26.5% (n= 27)	6.33±3.83
Mesenterik LN†	12.7% (n=13)	4.77±2.95
Bone	8.8% (n=9)	6.33±6.23
Abdomen	18.6% (n=19)	5.47±3.96
Head&Neck	10.8% (n=11)	4.73±3.49
Supraclaviculer LN†	6.9% (n=7)	5.7±3.05
Kidney	2% (n=2)	7.07±5
Paraaortic LN†	2% (n=2)	5.50±3.54
Anal canal	1% (n=1)	11
Rektosigmoid	24.5% (n=25)	16.12±8.31
Peritonitis carsinomotoza	1% (n=1)	22
Surrenal gland	3.9% (n=4)	3.75±2.87
Surgery area	22.5% (n=23)	12.48±5.01

* Standart uptake value; † Lymph node

Table 2. Agreement of PET/CT and CT on detection of pathology

a) Lung		
	CT	
PET/CT	Normal	Pathologic
Normal	59.8% (n=61)	0.0% (n=0)
Pathologic	33.3% (n=34)	6.9% (n=7)
Total	93.1% (n=95)	6.9% (n=7)
$\chi2$=11.2, p=0.001†, † Fischer's exact test value.		
b) Liver		
	CT	
PET/CT	Normal	Pathologic
Normal	53.9% (n=55)	2.0% (n=2)
Pathologic	14.7% (n=15)	29.4% (n=30)
Total	68.6% (n=70)	31.4% (n=32)
$\chi2$=46.6, p<0.001†, † Fischer's exact test value.		
c) Surgery area		
	CT	
PET/CT	Normal	Pathologic
Normal	75.5% (n=77)	2.0% (n=2)
Pathologic	14.4% (n=13)	9.8% (n=10)
Total	88.2% (n=90)	11.8% (n=12)
$\chi2$=28.8, p<0.001†, † Fischer's exact test value.		

Relationship between serum CEA levels and imaging modalities

Serum CEA levels were examined in 97 of the 102 patients and were found elevated in 27 (11.3-945 ng/ml) and normal in 70. Pathologic lesion was detected with PET/CT in 68 of the 70 patients with normal CEA levels. PET/CT results were normal in the remaining 2 patients.

CT was evaluated as 'pathologic' in 16 of the 27 patients with elevated CEA levels. Pathologic lesion was detected with CT in 45 of the 70 patients with normal CEA levels, and no lesion was detected in 20 patients.

Detection of Liver Metastasis of Colorectal Cancer with PET/CT and CT

The investigation included 30 patients whose liver biopsy, CT, and PET/CT data were available. For PET/CT, the sensitivity and specificity for the detection of liver metastasis were 88% and 92%, respectively. For CT, the sensitivity and specificity were 80% and 76%, respectively.

Assessment of Treatment Response after Restaging with PET/CT

An assessment of the treatment choice after restaging with PET/CT revealed that all patients were administered chemotherapy with a mean of 6.34±2.95 cycles. The rate of the patients who underwent radiotherapy was 16.7%, radiofrequency ablation 2.9%, and surgery 45.1%.

According to the SUV values, 95% of the patients partially responded to treatment, while 3.9% completely responded. The remaining 1.1% failed to respond.

Evaluation of PET/CT images after treatment revealed the responsive regions as mediastinum, lung, liver,

retroperitoneal lymph node, pelvic lymph node, bone, abdomen, head and neck, supraclavicular lymph node, kidney, para-aortic lymph node, anal area, rectosigmoid, and surgical site. Assessment of treatment response for lung, liver and surgery area are presented in **Table 3**.

Table 3. Treatment response assessment with FDG PET/CT

a) Lung		
	Post-treatment FDG PET/CT	
Pre-treatment FDG PET/CT	Normal	Pathologic
Normal	52.9% (n=54)	6.9% (n=7)
Patolojik	18.6% (n=19)	21.6% (n=22)
Total	71.6% (n=73)	28.4% (n=29)
$\chi 2$=21.4, p<0.001†, † Fischer's exact test value.		
b) Liver		
	Post-treatment FDG PET/CT	
Pre-treatment FDG PET/CT	Normal	Pathologic
Normal	49.0% (n=50)	6.9% (n=7)
Patolojik	16.7% (n=7)	27.5% (n=28)
Total	65.7% (n=67)	34.3% (n=35)
$\chi 2$=27.8, p<0.001†, † Fischer's exact test value.		
c) Surgery area		
	Post-treatment FDG PET/CT	
Pre-treatment FDG PET/CT	Normal	Pathologic
Normal	74.5% (n=76)	2.9% (n=3)
Patolojik	13.7% (n=14)	8.8% (n=9)
Total	88.2% (n=90)	11.2% (n=12)
$\chi 2$=21.4, p<0.001†, † Fischer's exact test value.		

DISCUSSION

Colorectal cancer is the most common type of gastrointestinal cancer. It is a significant cause of mortality and morbidity around the world, with more than 1 million people estimated to develop the disease per year (1-5). In Turkey, colorectal cancer ranks third after lung and breast cancers, and the incidence of the disease is 7.7% with a distribution of 59% male patients and 41% female. In the present study with a population of 102 patients, 38.2% were male and 61.8% were female.

Recurrence after treatment is common in colorectal cancer (15-19). In a study by Willkomm et al. (26), recurrence was reported to be seen within 3 years after primary tumor resection. Another study by Farrokh indicated the time to recurrence to be within the first 2 years after initial treatment (16). In the present study, the follow-up time was 11 to 50 months and the time to recurrence was 6 to 24 months.

Conventional imaging modalities such as USG, MRI, and CT are routinely used for determining the dissemination of disease and restaging when there are suspicious signs and symptoms suggesting recurrence in patients with colorectal cancer. Because these modalities have limitations in differentiating between inflammation/scar tissue occurring after surgery/radiotherapy and recurrence or metastasis, they are considered to have low sensitivity for restaging. CT also has limitations in detecting liver lesions, small-sized metastatic lymph nodes, and small-sized peritoneal malignancy (3-9).

F-18 FDG PET/CT is commonly used for diagnosis, staging, treatment response assessment, radiotherapy planning, and chemosensitivity assessment in many types of cancer (21-23). Higher glucose metabolism in cancer cells compared to normal cells results in increased FDG uptake, and, thus, tumor localization can easily be achieved. The superiority of PET/CT over other imaging modalities lies in its ability to demonstrate metabolic/functional changes at early stages in the absence of morphological change. Early detection of tumors with PET/CT imaging leads to early treatment and improved morbidity (20-23).

In a retrospective study of 50 patients by Metser et al. (17), FDG PET/CT and CT were compared with regard to the restaging of colorectal cancer. Based on the analysis of tumor presence, the sensitivity and specificity of PET/CT were reported as 98.1% and 75%, respectively, whereas those of CT were 66.7% and 62.5%, respectively. In the present study, recurrence at the pre-sacral area, lymph node <1cm, and liver metastasis around radiofrequency ablation focus were correctly identified with PET/CT, while missed by CT. In a study by Huebner et al. (23), the sensitivity and specificity of PET/CT for restaging was reported as 97% and 76%, respectively. In another study by Czerni et al. (2), the sensitivity of PET/CT for restaging was indicated as 88% . In the present study, the calculations of sensitivity and specificity of PET/CT and CT for restaging were not performed due to the lack of histopathology data for all patients. The pathologic lesion detection rates of PET/CT and CT for restaging purposes were determined as 98% and %64.7, respectively. In line with previous studies, our investigation corroborated the superiority of PET/CT in detecting tumor recurrence.

It is known that the most common site of metastasis for colorectal cancer is the liver. Synchronous liver metastasis rate during primary tumor resection is 10-25%. Liver metastasis rate within 2 years following tumor resection without synchronous metastasis was reported to be 20-50% (20,21). In our investigation, liver pathology was present in 44%, which was similar to previous studies. In a study by Wiering et al. (3), the sensitivity and specificity of PET/CT in detecting liver metastasis were 79.9% and 92.3%, respectively, whereas those of CT were 82.7% and 84.1%, respectively. In another study by Schlag et al. (17), the sensitivity and specificity of FDG PET/CT in detecting liver metastasis were 91% and 100%, respectively, whereas those of CT were 74% and 85%, respectively. The study of Niekel et al. (27) reports both parameters as 97% for PET/CT, 88% and 93% for MRI,

respectively, and 84% and 95% for CT, respectively. In the present study, the sensitivity and specificity of PET/CT in detecting liver metastasis of colorectal cancer was 88% and 92%, respectively, whereas that of CT were 80% and 76%, respectively. These figures were in line with previous studies indicating a higher sensitivity and specificity for PET/CT.

The lung is the site where PET/CT is the most effective in detecting extra-hepatic metastases of colorectal cancer. Recent studies have shown that PET/CT can detect all lesions in the lung while CT can only detect 20%. The sensitivity of CT in detecting para-aortic and portal lymph node metastasis is 46% while that of PET/CT is 77%. The reliability of CT and PET/CT is much lower for bone and peritoneal metastasis, and laparoscopy is the best option to assess peritoneal metastasis before laparotomy (18,19-21). In many cases, local recurrence at the primary site of colorectal cancer cannot be identified due to the prior surgery and, sometimes, postoperative changes. Studies have shown that PET/CT is 93% successful in detecting the local recurrence of colorectal cancer, while CT is 50%. PET/CT's limitation lies in not differentiating increased FDG uptake due to chronic infection and tumors.

In the present study, a localization-based comparison of PET/CT and CT revealed that PET/CT is significantly superior to CT in detecting lesions in the mediastinum, lung, rectosigmoid, peritoneum, suprarenal gland, and the surgical site. PET/CT is important in the detection of small lymph nodules, early osseous deposits and inflammatory changes due to treatment. But, PET/CT has imitations on detecting subcentimetric hepatic and lung nodules (28).

Elevated serum CEA levels are observed in approximately two-thirds of the patients with colorectal cancer, meaning that it is the earliest sign to suggest the disease or its recurrence among other diagnostic symptoms. The sensitivity of CEA in detecting recurrence is 70-80%, but lesion-based examination has revealed that CEA has lower accuracy in detecting local recurrences and lung metastases. Conventional imaging modalities such as CT and MRI can localize recurrence 3-9 months after the increase in CEA levels (10,29-32). With its functional imaging capabilities, FDG PET/CT is more sensitive compared to other modalities when CEA levels are increased. FDG PET/CT has 65-75% diagnostic accuracy in cases suggesting recurrence with elevated CEA levels despite negative results with conventional imaging (32). Recent studies have reported its positive predictive value as 89-95% and negative predictive value as 85-100% in patients with high CEA levels (10). In any case, PET/CT is recommended as a more accurate diagnostic tool in patients with normal CEA levels. In a retrospective study, Sarıkaya et al. (11) examined the PET findings of colorectal patients with normal CEA levels and reported a positive predictive value of 88.8% for PET/CT, particularly in liver metastasis. In the present study, serum CEA levels data of 92 among the 102 total patients were available, and 70 (72.2%) of these were within the normal range whereas 27 (27.8%) were elevated. Pathologic lesion was detected via PET/CT in 68 of the 70 patients with normal CEA levels, suggesting that PET/CT is superior in detecting colorectal cancer or its recurrence, which was in line with previous studies. The comparison of CEA levels and CT results in the present study showed that CT detected pathology in 25 of the 70 patients with normal CEA levels, and in 16 of the 27 patients with elevated CEA levels. Our investigation yielded no significant difference between CT and serum CEA with regard to detecting recurrence.

Anatomic imaging modalities such as CT and MRI often fail to assess treatment response after restaging due to conditions such as treatment-induced necrosis and inflammation. FDG PET/CT is successful in this regard. However, the accuracy of PET/CT imaging depends on allowing sufficient time for the disappearance of benign metabolic activity, which can develop after treatment. The longer the time allowed prior to the imaging, the specificity of FDG PET/CT is higher.

Our study suggested FDG PET/CT is considered a more accurate diagnostic tool compared to other imaging modalities for restaging and treatment response assessment in cases of colorectal cancer with suspected recurrence on follow-up after treatment.

ETHICAL DECLARATIONS

Ethics Committee Approval: Due to the regulations and the requriements which are subject to our study at the date of application did not enforce seperate ethical approval for retsospective studies. Our study was approved by Başkent University Medicine and Health Sciences Research Board of the institution within these circumstances that are explanied above (Date: 02.08.2011, Decision No: KA11/166).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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